REMARKS

In the Action, claims 1-20 are rejected. In response, claim 1 is amended to include the subject matter of claim 3. Claims 2 and 3 are cancelled.

In view of these amendments and the following comments, reconsideration and allowance are requested.

The Rejections

Claims 1, 2, 7, 12-15 and 17-20 are rejected under 35 U.S.C. § 103(a) as being obvious over DE 29922585, WO 02/083194 to Beam et al. and U.S. Patent No. 6,210,715 to Starling et al. The rejection is based on the position that it would have been obvious to modify the prior patents in a manner to obtain the claimed invention. The amendment to claim 1 to include the subject matter of claim 3 obviates this rejection.

Claims 3, 4, 11, 12 and 16 are rejected as being obvious over DE '585, Beam et al., Starling et al. and WO 92/21302 to Johansson. The Action suggests that it would be nothing more than routine optimization based on the disclosure of Starling et al. to modify the sintering temperature, thereby modifying the particles of DE '585, Beam et al. and WO '302. Applicants respectfully submit that Starling et al. provides no suggestion to one skilled in the art to modify the sintering temperature as suggested in the Action. Moreover, Starling et al. does not disclose or teach how to obtain a bone formation agent having three discrete pore sizes as recited in amended claim 1.

Initially, Applicants note that the terms "pores" and "channels" as used in the Action and the cited art are not synonymous or interchangeable. Channels are typically used to define passages that traverse the sintered ceramic material from one end to the other. Pores on the other

hand are holes or voids that do not traverse the ceramic material but define empty space within the sintered regions of the ceramic material. Thus, the reference to the channels in the Action does not reflect the terms as commonly used by one skilled in the art and does not define the pores of the claimed invention.

The Action relies on Starling et al for allegedly teaching different pore sizes and how to modify pore sizes. The Action suggests that the claimed pore size distribution could be achieved by simply adjusting the sintering temperature. However, one skilled in the art would recognize that attaining a specific pore size and pore size distribution cannot be obtained by simply modifying the sintering temperature. Furthermore, adjusting the sintering temperature alone is not capable of producing the three discrete pore sizes of the claimed invention. The suggestion in the Action that modifying the sintering temperature alone would obtain the claimed bone formation disregards the complex chemistry of calcium phosphate bioceramics.

Moreover, the modification of the pore sizes disclosed by Starling et al. is limited to a single pore size range. It is not possible to attain the claimed porosity having three discrete pore sizes by simply altering the sintering conditions. Applicants enclose as Attachment I the article by de Groot et al., *Handbook of Bioactive Ceramics*, Vol. II, Calcium Phosphate and Hydrocyl Apatite Ceramics, CRC Press, 1990. As disclosed on pages 7-9 and Figures 2-5 of de Groot et al., there are various calcium phosphates that can be obtained at high temperatures. Accordingly, the claimed invention pure phase calcium phosphate can only be attained if the sintering process is performed at a certain temperature, partial pressure of water vapor in the ambient atmosphere and the exact calcium-phosphorous ratio. Thus, one skilled in the art would recognize that simply changing the sintering temperatures does not inherently produce the claimed three

discrete ranges of pore sizes. The phase transitions will occur resulting in mixed phase calcium phosphates. Starling et al. in column 4, lines 40-44, expressly teach mixed phase macrospheres.

Moreover, Figure 6 on page 9 of de Groot et al. discloses that more complete sintering results in shrinkage of the particle while producing smaller micropore volume. Thus, the optimization as suggested in the Action would not result in the claimed bone formation agent comprising sintered particles of calcium phosphate having at least three discrete pore size distributions and an interconnecting porosity limited to pore sizes less than 10 μm as in amended claim 1. The changes in the sintering temperatures as suggested in the Action produce a more highly closed porosity composition with fewer and smaller interconnecting pores. Thus, modifying the temperature according to Starling et al. as suggested in the Action would lead to a dense product that does not possess the claimed porosity.

The resulting densified particles obtained by modifying the sintering temperature as disclosed in Starling et al. are demonstrated by the attached images A and B enclosed as Attachment II. Image A shows the bone formation according to the present invention. Image B shows the calcium phosphate by modifying the sintering temperature and time to effect complete sintering as suggested by the Action and disclosed in Starling et al. Image B shows a more dense composition with smaller pore sizes. The microscopic images A and B demonstrate that modifying the pore size by changing the sintering temperature as suggested in the Action does not inherently result in the claimed invention. In contrast, a more complete sintering leads to a dense composition that is void of the claimed porosity having three discrete ranges of pore sizes.

Based on the above, the claimed pores sizes of the bone formation agent is not simply an optimization as suggested in the Action. Moreover, the claimed bone formation is not an optimization simply by modifying the sintering temperature as disclosed in Starling et al. and as

suggested in the Action. Even if one were to modify the sintering temperature according to Starling et al. as suggested in the Action, the resulting product would not be the claimed invention. Moreover, one skilled in the art would have no reasonable expectation of success in attaining the claimed product simply by modifying the sintering temperature according to Starling et al.

The Action notes that Starling et al. discloses a coating on the substrate which is not relevant to the claimed invention. Thus, Example 3 of Starling et al. which relates to porous calcium phosphate coatings for bonding to the substrate surfaces of hollow or solid beads does not suggest the claimed invention and does not suggest modifying the sintering steps in order to obtain the claimed invention. Starling et al. in Example 3 discloses the calcium phosphate coatings on a substrate of calcium phosphate, glass, oxide ceramics, polymers, proteinaceous materials or composite materials. Example 3 of Starling et al. teachings a porous structure of a calcium phosphate coating that is completely unrelated to the claimed bone formation agent. Examples 6 and 10 of Starling et al. do not read on or suggest the claimed bone formation agent either alone or in combination with the other cited patents. Claims 6 and 10 relate to aggregates of microspheres with completely different porosity and particle sizes from that defined in claim 1. Accordingly, one of ordinary skill in the art would not be motivated to modify the process of DE '585 and/or Beam et al. according to Starling et al. with a reasonable expectation of success in obtaining the claimed bone formation agent.

Starling et al. teaches microspheres that are essentially spherical where the porosity is controlled by the sintering step. As noted above, and as demonstrated in the microscopic images attached hereto, the more complete sintering of Starling et al. does not lead to the claimed bone formation agent and the claimed discrete pore sizes. Therefore, modifying DE '585 according to

Starling et al. may modify the pores of DE '585 by more complete sintering but would not lead to the claimed invention. In contrast, a more complete sintering of DE '585 as suggested in the Action would result in a dense calcium phosphate particle that lacks the claimed porosity. In addition, the more complete sintering as suggested in the Action may result in a mixed phase calcium phosphate due to the phase transitions that occur at high sintering temperature and/or extended sintering time.

DE '585 and Beam et al. do not suggest or disclose a bone formation agent having an absence of interconnecting macropores as in claim 1. Contrary to the suggestion in the Action, the claimed porosity, particle size and phase purity cannot be attained simply by modifying the pores of DE '585 and Beam et al. by simply changing the sintering temperature. Thus, even if one were to modify the sintering temperature according to Starling et al., the result would not be the claimed invention.

Applicants respectfully submit that the rejection is based on selecting certain features from the cited patents and piecing them together in light of the present invention. However, this does not establish that one skilled in the art could arrive at the claimed invention or that it would have been obvious to modify or combine the teachings of the cited patents without using Applicants' specification as a guide. For the reasons discussed above, the cited patents either standing alone or in combination cannot be adapted to arrive at the claimed invention.

The cited patents and the de Groot et al. article disclose large interconnecting macropores as an essential technical feature of bioceramics. Thus, the cited patents effectively teach away from the claimed invention. Claim 1 specifically limits the interconnecting pores to less than 10 μm.

WO '302 does not disclose or suggest interconnecting micropores having a pore size of less than 10 μm. WO '302 specifically discloses the pores being distributed in different parts of the implant. There is no suggestion of three distinct pore sizes in the particles within the claimed range of 0.5 to 10 μm, 10 to 100 μm, and 100 to 5,000 μm where the particles have interconnecting pores limited to less than 10 μm. WO '302 either standing alone or in combination with DE '585, Beam et al. and Starling et al. do not disclose or suggest the claimed three discrete particle sizes and interconnecting pore size.

Accordingly, claim 1 and the claims depending therefrom are not obvious.

Claims 5, 8-10 and 18-20 are rejected under 35 U.S.C. § 103(a) as being obvious over DE '585, Beam et al., Starling et al., WO '302 and U.S. Patent No. 6,521,249 to Sapieszko. Sapieszko is cited for disclosing inorganic shaped bodies for bone grafting. Sapieszko relates to inorganic shaped bodies for beta-tricalcium phosphate having a porosity of 30-90% but clearly does not provide the deficiencies of DE '585, Beam et al. and Starling et al. for the reasons discussed above. Sapieszko discloses pores being uniform and produced according to a template technique using a sponge as a substrate. The sponge is imbibed with a reaction solution containing calcium phosphate and the organic component of the sponge is burned to produce the calcium phosphate framework corresponding to the pores of the sponge. The pores of the sponge generally have round shapes as shown in the figures of Sapieszko.

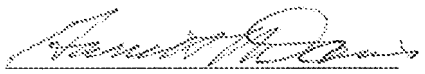
Sapieszko has no relation to DE '585, Beam et al., Starling et al. and WO '302. The Action relies on Starling et al. for adjusting the sintering temperature to attain the desired pore size. The pore size disclosed in Sapieszko cannot be obtained according to Starling et al. such that it would not have been obvious to one skilled in the art to combine the teachings of DE '585, Beam et al., Starling et al., WO '302 and Sapieszko.

Sapieszko also does not disclose the calcium phosphate containing 95% alpha-tricalcium phosphate, beta-tricalcium phosphate, octacalcium phosphate, alkali metal-modified and/or alkaline earth metal-modified tricalcium phosphate, calcium diphosphate, carbonate apatite of type B, calcium-deficient hydroxyapatite or mixtures thereof as in claim 5, either alone or in combination with the features of amended claim 1. Sapieszko does not disclose the geometric shapes of claims 8-10, the discrete pore size distribution of claims 11 and 12, and the shaped body of claims 13-15, the pore size distribution of claim 16, the surface component of claim 17, or the shaped body of claims 18-20. Accordingly, these claims are not obvious over the combination of the cited patents.

Claim 6 is rejected under 35 U.S.C. § 103(a) as being obvious over the combination of DE '585, Beam et al., Starling et al., WO '302, Sapieszko and further in view of Trisi et al. Trisi et al. is cited for disclosing pure phase beta-tricalcium phosphate. Applicants submit that the combination of six cited references does not render the claims obvious to one of ordinary skill in the art. Furthermore, Trisi et al. provides no suggestion to one skill in the art to use beta-tricalcium phosphate having a phase purity of 99% by weight in the bone formation of claim 1. Accordingly, claim 6 would not have been obvious over the combination of the cited patents.

In view of the above comments, the claims are submitted as being in condition for allowance. Accordingly, reconsideration and allowance are requested.

Respectfully submitted,



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CHEMISTRY OF CALCIUM PHOSPHATE BIOCERAMICS

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INTRODUCTION

The modern era of calcium phosphate-based bioceramics started 20 years ago (1969) with the first successful publication by Levitt et al.[1] in the then newly founded *Journal of Biomedical Materials Research*. They stated that although apatites had undergone intensive investigation for many years, lack of effective methods of forming apatite powders into solid shapes had prevented (up to that time) the study of potential uses of calcium phosphate bioceramics.

Since then, calcium phosphate bioceramics have gained a distinct place in the biomaterials research field, as can be judged by the large number of publications and presentations. For example, at the World Biomaterials Conference in Kyoto, held in 1988, more than 100 presentations were related to calcium phosphate.[2]

In addition to the regular scientific literature, many patents have been filed. In 1987 alone there were 126,[3] their object being the manufacture of prostheses or prosthetic materials with properties like those of natural bone.

It is interesting to note that while most scientific publications deal with animal and clinical testing, and less than one third with technical experimental results, patents deal almost exclusively with preparation methods, technical innovations, and construction of specific implants. The extensive patent filings emphasize the high expectations that the medical community has of calcium phosphate biomaterials, and therefore we believe that clinical applications will be even more important in the future than they are already.

In this chapter, we intend to describe one aspect of calcium phosphates, namely, their physicochemical properties. To do that we will first discuss the stability of various calcium phosphate phases at room temperature as well as at temperatures of 1000°C or more, under different ambient conditions. Based on this information, we proceed to methods of preparation of dense and porous calcium phosphate bioceramics and their crystallographic and mechanical properties.

In addition, we summarize the current data on biocompatibility. In conclusion, we summarize current and future clinical developments as derived from the information presented in the preceding paragraphs.

PHASES AT ROOM TEMPERATURE

PHASES OF CALCIUM AND PHOSPHATE ONLY, IN AQUEOUS EQUILIBRIUM

Since any practical, i.e., clinical, use of calcium phosphate bioceramics involve contact with water (and other components present in body fluids), it is important to know the stability of materials composed of calcium and phosphate in the presence of water. Although calcium phosphates are usually obtained by sintering at high temperatures, sometimes under the exclusion of water vapor, it is the stability at ambient and body temperatures that determines their fate after implantation. Since solid-state reactions hardly ever occur at room temperatures, solid, unstable phases will only react at their surfaces. If the surface continually dissolves the whole implant may dissolve. If surface reactions lead to the formation of a thin layer of a second stable phase, the virtual absence of solid-state reactions causes the unstable solid to be stabilized.

As Driessens[4] showed, there are only two calcium phosphate materials that are stable

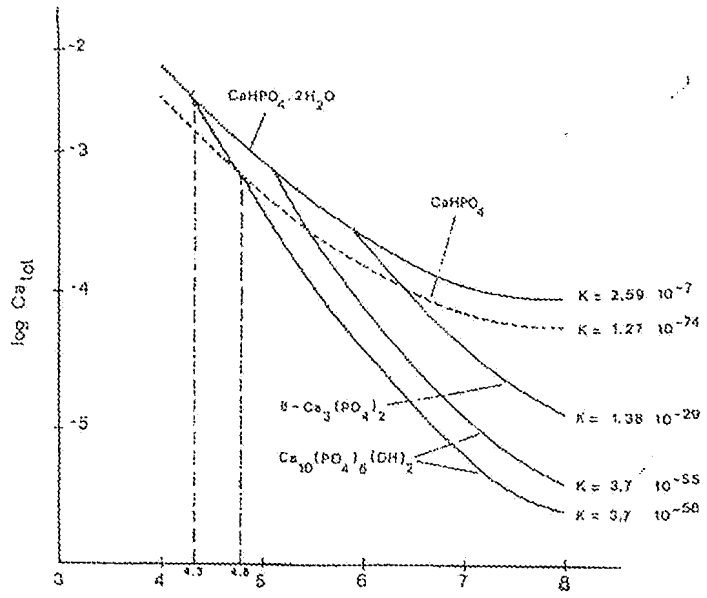

FIGURE 1. Solubility of various phases in the system $CaO-P_2O_5-H_2O$ as function of pH (horizontal axis).

at room temperature when in contact with aqueous solution, and it is the pH of the solution that determines which one is the most stable. At a pH lower than 4.2, the component $CaHPO_4 2H_2O$ (dicalcium phosphate) is the most stable, while at higher pH (> 4.2), hydroxylapatite ($Ca_{10}[PO_4]_6[OH]_2$) is the stable phase.

This means that at thermodynamic equilibrium the situation is uncomplicated: only dicalcium phosphate (at pH < 4.2) or hydroxylapatite (at pH > 4.2) can be found in contact with aqueous solutions (Figure 1). However, at higher temperatures, many other phases can be formed that, when cooled, keep their thermodynamically unstable composition due to the absence of solid-state reactions. The most relevant ones are β-tricalcium phosphate ($Ca_3[PO_4]_2$) and tetracalcium phosphate ($Ca_4P_2O_9$). Others, such as α-tricalcium phosphate, have received only passing interest in the biomaterials field and will not be discussed in this chapter.

Adam et al.[5] discussed in their publication on solubilities of calcium phosphate biocermics that phases other than hydroxylapatite will have a surface gradually covered with hydroxylapatite. Newesely[6] described these reactions as:

$$4Ca_3(PO_4)_2(s) \rightarrow Ca_{10}(PO_4)_6(OH)_2(s) + 2Ca^{2+} + 2HPO_4^-$$

and

$$3Ca_4P_2O_9(s) + 3H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2(s) + 2Ca^{2+} + 4OH^-$$

respectively, for β-tricalcium phosphate and tetracalcium phosphate.

An initial dissolution of the surface is followed by reprecipitation, assuming that, near the surface, a saturated solution exists with respect to the unstable phases: this solution should then be supersaturated with respect to the stable (hydroxylapatite) phase.

This gradual transition toward an hydroxylapatite surface explains the change in solubility of a β-tricalcium phosphate surface to a value approaching the solubility of hydroxylapatite, as can be concluded from the findings of Adam et al.[5] and Klein et al.[7]

From the above reactions it also follows that β-tricalcium phosphate decreases the pH while being covered with a thin apatite layer (pK value of $CaHPO_4$ is 2.4), while tetracalcium phosphate does the opposite ($Ca[OH]_2$ is a strong base). Since for both β-tricalcium phosphate and tetracalcium phosphate the solubility decreases with increasing pH, one may reason that, if no buffering takes place, not only the gradual phase change into hydroxylapatite influences the solubility, but also the associated change in pH. The solubility of β-tricalcium phosphate should then increase, and that of tetracalcium phosphate should decrease.

Klein et al.[7] compared the influence of buffering with nonbuffering, and they found that incubation of various calcium phosphates in unbuffered solutions resulted in a low solubility for tetracalcium phosphate, hydroxylapatite, and β-tricalcium phosphate, in agreement with Adam et al.[5] In a buffered solution, the solubility rate was much higher. In the section on preparation methods, we discuss this aspect further in relation to biodegradation.

We have not yet taken into account a further complication, the presence of micropores. Depending on the preparation process, a ceramic may be produced in which individual small particles (several microns in diameter) are only partially connected with each other, thereby leaving small spaces, micropores, between them. These partial connections, called necks, are usually characterized by a poor crystalline structure and are more soluble than the bulk ceramics. Due to their tiny dimensions, complete dissolution of these necks may occur if they consist of unstable phases, such as β-tricalcium phosphate, before reprecipitation of apatite stops this process. In that case, microporous blocks may simply disintegrate into small powder particles, thus exhibiting another type of instability.

PHASES OF CALCIUM AND PHOSPHATE AND OTHER IONS, IN AQUEOUS EQUILIBRIUM

Both Ca^{2+} and PO_4^{3-} ions, as well as the OH^- group in hydroxylapatite, can be replaced by other ions, several of them present in physiological surroundings. A well-known ion is fluor, leading to fluor-containing apatites

$$Ca_{10}(PO_4)_6(OH)_{2-x}F$$

$$0 < x < 2$$

Another well-known ion is carbonate (CO_3^{2-}) which, when incorporated into hydroxylapatite yields the so-called carbonated apatites with various chemical formulas. Two published[8] examples are

$$Ca_{10}(PO_4)_6(OH)_{2-2x}(CO_3)_x$$

and

$$Ca_{10-x+y}(PO_4)_{6-x}(CO_3)_x(OH)_{2-x+2y}$$

$$0 < x < 2$$

$$0 < y < 1/2\ x$$

The first formula suggests a partial replacement of the OH group only, while the second one corresponds with a partial replacement of both PO_4 and OH groups.

More common is the incorporation of both sodium ions (Na^+) and carbonate ($CO_3^=$) ions or both potassium ions (K^+) and carbonate ions. For example, the respective formulas are reported[4] to be

$$Ca_{10}Na_{2/3x}(PO_4)_{6-x}(CO_3)_x(H_2O)_y(OH)_{2-1/3x}$$

$$0 < x < 3$$

$$0 < y < x$$

and

$$Ca_{10-1/2x}K_{1/2x}(PO_4)_{6-1/2x}(CO_3)_x(OH)_{2-1/2x}$$

$$1 < x < 3$$

Magnesium ions stabilize β-tricalcium phosphate; the formula of Mg containing β-tricalcium phosphate is

$$Ca_{3-x}Mg_x(PO_4)_2$$

$$0 < x < 2/3$$

Besides these, more or less "physiological" phases, many other foreign ion-containing calcium phosphates can be conceived. For biomedical purposes, the materials of interest are (1) carbonated apatites, beause of their assumed similarity to bony apatite; (2) fluor apatites, because of their decreased solubility in aqueous solutions; and (3) magnesium tricalcium phosphate, due to its increasesd stability with respect to "pure" tricalcium phosphate.

PHASES AT HIGH TEMPERATURE

High-temperature stability of calcium phosphates is best illustrated by the phase diagrams shown in Figures 2 through 5. We focus on temperatures at which sintering processes usually take place, i.e., in the range of 1000 to 1500°C.[6]

Figure 2 shows that if the ambient atmosphere contains no water, various calcium phosphates can be found at high temperatures, such as tetracalcium phosphate (= C_4P), α-tricalcium phosphate (α-C_3P), monetite (= C_2P), and mixtures of calcium oxide (CaO) and C_4P. Hydroxylapatite is not stable under these conditions. If the partial water pressure is increased form 0 to 500 mmHg, as shown in Figure 3, then the situation is quite different: hydroxylapatite can be found (= Ap). If the ratio Ca/P is not exactly equal to 10/6, a wide range of apatite-containing mixtures is thermodynamically stable, e.g., tetracalcium phosphate, tricalcium phosphate and calcium oxide (CaO).

The two phase diagrams, Figures 2 and 3 stress the importance of temperature, exact Ca/P ratio, and partial pressure of water vapor in the ambient atmosphere in the determination of stable phases (β-tricalcium phosphate turns into α-tricalcium phosphate around 1200°C; the latter phase is considered to be stable in the range 700 to 1200°C).

The importance of partial water pressure is shown more clearly in Figure 4. This diagram shows, for example, that for a Ca/P ratio higher than 10/6, at a temperature of 1300°C (10^4/

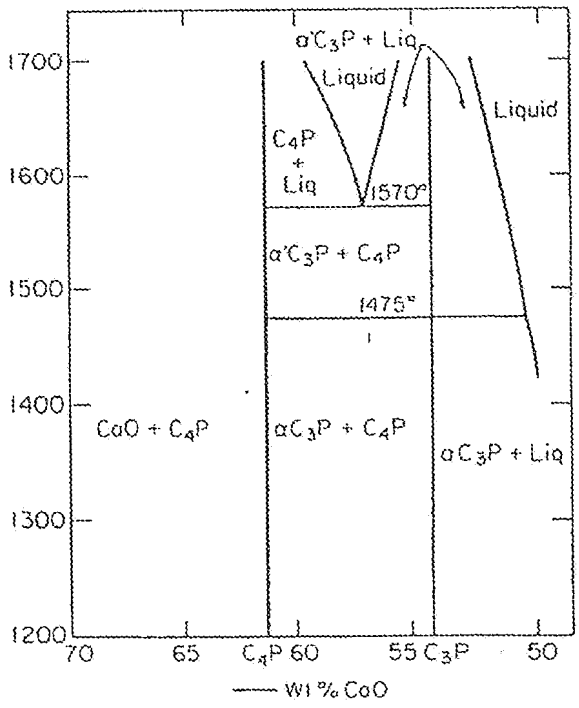

FIGURE 2. Phase diagram of the system CaO-P_2O_5 at high temperatures (vertical axis: temperature in °C). No water present.

T = 6.4, if T is expressed in °K), the stable phase is C_3P + C_4P if the vapor pressure is 1 mmHg (log P_{H_2O} = 0). The stable phases are Ap + C_4P at 10 mmHg. Mixtures of Ap + CaO are stable at pressures of around 100 mmHg. Thus, with a Ca/P ratio exceeding that of apatite by only a few percent, stable phases can vary from C_3P + C_4P (log P_{H_2O} = 0), Ap + C_4P (log P_{H_2O} = 1), and Ap + CaO (log P_{H_2O} = 2).

The part of the Ca/P phase diagram that is most crucial is shown in Figure 5. As in Figure 4, T_1 and T_2 are water vapor pressure-dependent phase transitions, showing that, besides temperature and Ca/P ratio, this pressure is also of utmost importance in the determination of stable phases.

Several phase transitions may take days or longer, especially at temperatures below 1000°C. Therefore, it is not always easy to predict which phases, stable at high temperatures, will remain so at room temperature.

In the previous paragraphs we discussed the stability of calcium phosphate at room temperature and in an aqueous environment. We found that the only stable phases are either brushite ($CaHPO_4 \cdot 2H_2O$) (at pH 4.2) or hydroxylapatite (at pH ≳ 4.2). Hence, except for hydroxylapatite, most phases stable at high temperature will gradually undergo a phase transition (to hydroxylapatite, if the pH is physiological). It is not surprising then that β-tricalcium phosphate has been shown to transform into hydroxylapatite after incubation in aqueous solution at body temperature.[9]

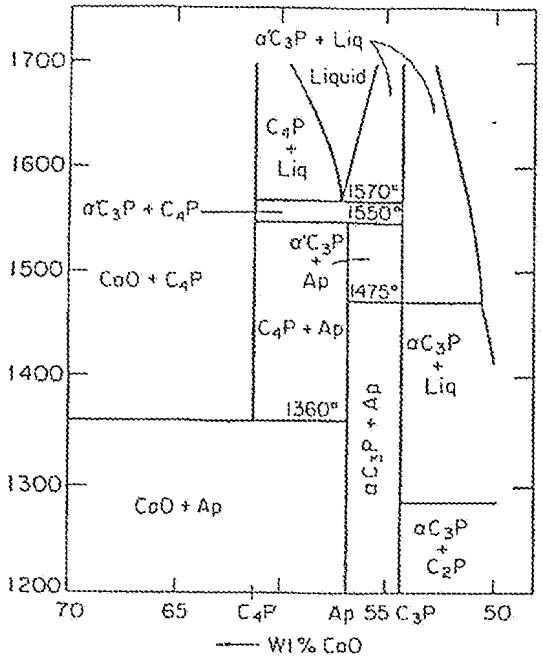

FIGURE 3. Phase diagram of the system Cao-P_2O_5 at high temperature (vertical axis: temperature °C). Water vapor: pH_2O = 500 mmHg.

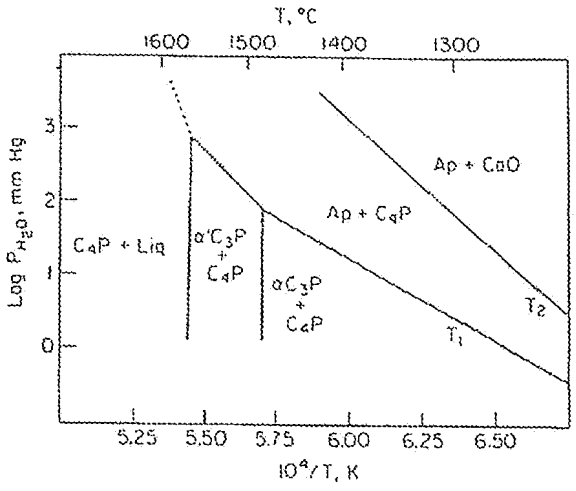

FIGURE 4. Influence of ambient water vapor pressure (vertical axis: PH_2O in mmHg) on phase composition.

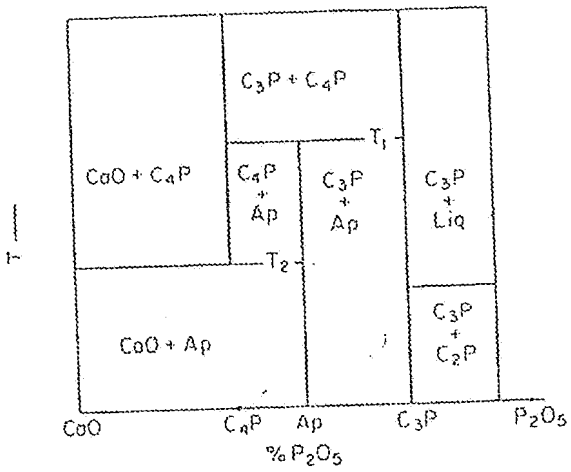

FIGURE 5. Enlarged part of Figure 3. Instead of 1360°C, we use T_2, and instead of 1475°C we use T_1, to indicate that these values hold only for pH_2O = 500 mmHg.

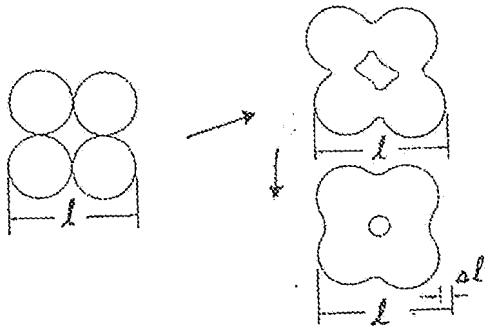

FIGURE 6. Simplified process of sintering: particles (left) are slightly fused together after incomplete sintering (upper right: microporosity is high). More complete sintering leads to smaller micropore volume and more shrinkage ($-\Delta l$, lower right).

PREPARATION METHODS — DENSE AND POROUS CERAMICS[10]

DENSE CERAMICS OF CALCIUM PHOSPHATE

Dense ceramics are usually made by compressing a powder into a pellet, which thereafter is subjected to a heat treatment that causes the powder particles to fuse together by means of solid-state diffusion. (Melting them together is not possible as phase diagrams in Figures 2 and 3 show, e.g., the melting processes are incongruent.) Such a process is called sintering and is schematically depicted in Figure 6. Depending on variables such as sintering temperature, time, and particle size distribution, a dense shape can thus be produced, dense being defined as less than 5% (in volume) porous. A modification of this standard technique has been reported [10] by using hot pressing. In this technique a powder is simultaneously compressed and fired, and according to the developers, excellent products are thus obtained.

However, no significant improvement in properties as compared with conventional techniques were found. Since hot pressing is a very expensive technique, little additional work has appeared.

Powder, if not obtained from industry, can be easily prepared in the laboratory: mixing ammonium phosphate and calcium nitrate results in a precipitate, which results in the composition of stoichiometric hydroxylapatite, if variables such as pH and various ionic concentrations are well chosen. Similarly, a powder with the stoichiometrical composition of tricalcium phosphate can be obtained. From the discussion in the previous paragraphs it follows that such a composition must consist of hydroxylapatite and brushite. Firing these powders results in sintered hydroxylapatite and tricalcium phosphate, respectively.

Techniques other than sintering have been reported, but thus far they have not gained wide acceptance. Nevertheless, it is worthwhile to mention a few that may be of future interest. Nature provides many minerals in the form of large mono- or polycrystalline samples, examples being fluorapatite and various calcium carbonates. Such crystals can also be prepared in the laboratory by slowly cooling a melt or from concentrated solution, accompanied by seeding at the appropriate temperature. In this way, polycrystalline pieces of hydroxylapatite have been obtained of almost 1 cm in length. Another technique duplicates biological structures of calcium carbonate by replication as calcium phosphate.[13] So-called "replamineform" implants are pieces of coral, transformed into calcium phosphate by hydrothermal reactions. Both hydroxylapatite and tricalcium phosphate samples can be prepared in this manner. Powder-liquid systems have been suggested, based on gypsum and calcium phosphate, that can be shaped at room temperature.[16] Finally, two very new techniques should be mentioned: so-called "detonation" sintering and "microwave" sintering.[12] In the first process, an explosive is used to compact a starting powder. Due to the high friction, the powder particles melt superficially, resulting in simultaneous sintering. The whole process lasts less than 1 μ (10^{-6}) s. Densities of more than 95% are reported for aluminum oxide, and in our laboratories we have initiated a research project to achieve the same densities for hydroxylapatite powders. The second process involves the use of a microwave oven to heat the ceramic powder or green body. Since the heat is generated within the sample, more uniform properties throughout the sintered body can be expected. Experiments with aluminum oxide have shown that a temperature of 1500°C can be reached within 1 or 2 min. This process may be of use in the production of bioceramics of calcium phosphate as well, especially since solid state phase transitions lasting longer than a few minutes could be avoided.

POROUS CERAMICS OF CALCIUM PHOSPHATE[13]

Several methods are used to introduce macropores into a bioceramic. Holes can be drilled into the fired body, but a more appropriate technique is based on mixing the starting powder with appropriately sized organic powders, threads, or sponges. These organic additives burn out and leave behind their replicas as voids when the green body is heated up to sintering temperatures. Alternatively, a powder may be turned into a slurry with hydrogen peroxide, the dissociation of which at higher temperatures also leaves pores in the green body. A last method is to apply the replica method to porous bodies.

CRYSTALLOGRAPHICAL AND MECHANICAL PROPERTIES

CRYSTALLOGRAPHY

Since hydroxylapatite is the only stable phase of calcium phosphate in an aqueous environment at neutral pH, we first describe the crystallographic properties of this material. Hydroxylapatite is a specific solid of a large class with the general formula $M_{10}(XO_4)Z_2$, where M is a bivalent metal ion, XO_4 is a trivalent negative ion, and Z is a monovalent

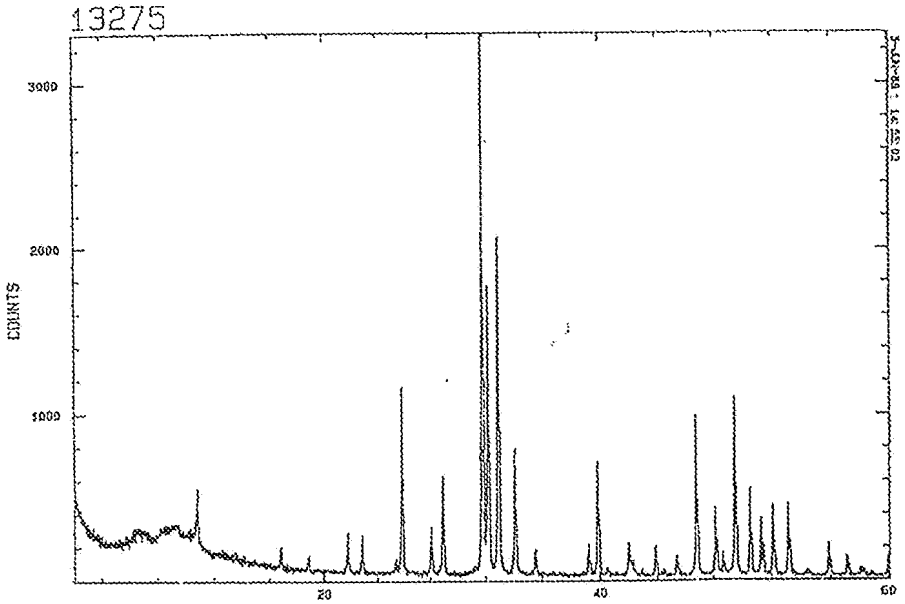

FIGURE 7. X-ray diffraction pattern of well-crystallized hydroxylapatite (horizontal axis: 2 θ).

negative ion. The metal ion can be Ca^{2+}, but also Pb^{2+} and Cd^{2+}, while examples of XO_4 are PO_4^{3-} and MnO_4^{3-}. The monovalent Z ion may be OH^-, F^-, and others.

Metal and monovalent Z positions may be partially "filled" with vacancies, such that the electroneutrality of the crystal is preserved. Another modification is the appearance of vacancies combined with substitutions: $Ca_8V_2(PO_4)_4(CO_3)_2V_2$ is an example, V being the vacancy. Hydroxylapatite possesses a hexagonal structure with a $P6_3/m$ spacegroup and cell dimensions a = b = 9.42 Å, and c = 6.88 Å, where $P6_3/m$ refers to a spacegroup with a sixfold symmetry axis with a threefold helix and a microplane.

A typical X-ray diffraction pattern of powdered and sintered hydroxylapatite is shown in Figure 7. Crystal structures of related calcium phosphates are also well defined. β-Tricalcium phosphate shows an X-ray pattern (Figure 8) consistent with a pure hexagonal crystal structure, although the related α-tricalcium phosphate is monoclinic.

Tetracalcium phosphate is also a monoclinic substance. A name would be tetracalcium monoxide diphosphate. An X-ray diffraction pattern (see Figure 9) shows distinct differences from the other patterns.

It is difficult to define an "optimal" degree of crystallinity. If one tries to imitate bone mineral, then an implant would be characterized by the presence of small crystals, of 100 nm or less, that constitute bone mineral. X-ray diffraction patterns should then be rather broad.[14] On the other hand, a pure technological approach is toward well-crystallized samples with (almost) no line broadening, allowing the end product to be clearly defined. We believe the biological approach to be preferable: the degree of crystallinity should approach that of the mineral in natural bone.

MECHANICAL PROPERTIES

Both tensile and compressive strength of calcium phosphate ceramics depend on the portion of the total volume of the material occupied by interstices. These interstices, or

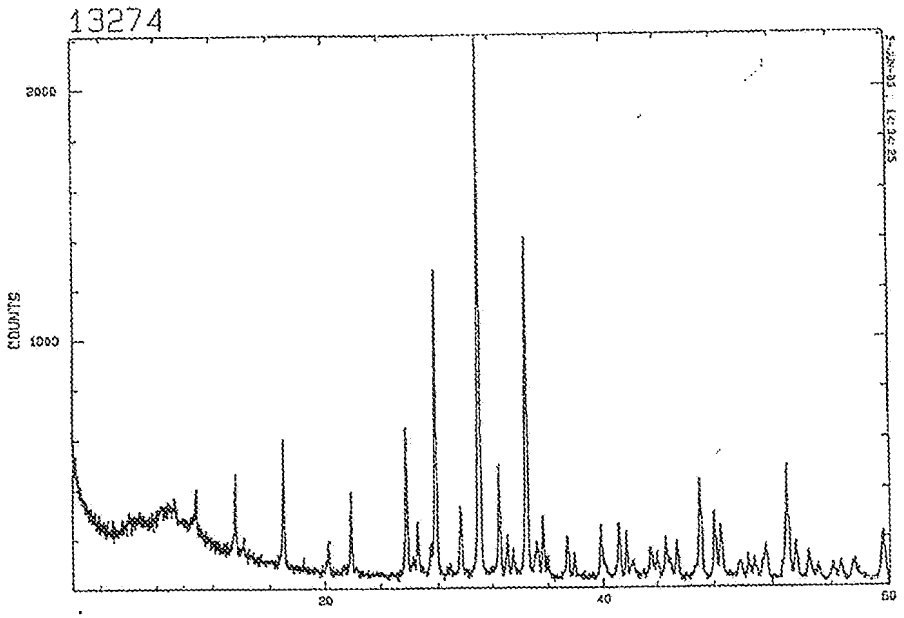

FIGURE 8. X-ray diffraction pattern of well-crystallized tricalcium phosphate (horizontal axis: 2 θ).

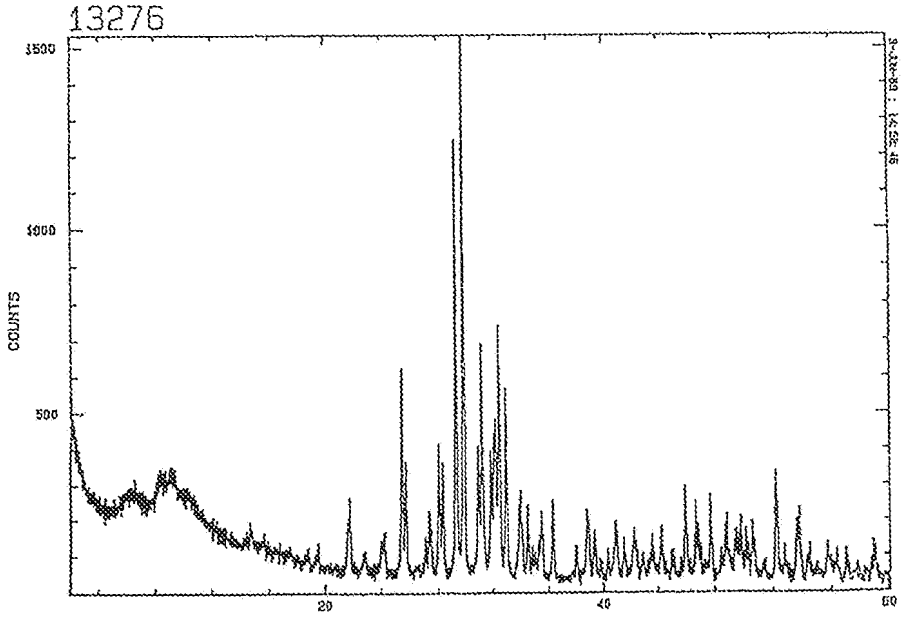

FIGURE 9. X-ray diffraction pattern of well-crystallized tetracalcium phosphate (horizontal axis: 2 θ).

pores, are classified as either micropores (with diameters of about 1 μm, due to incomplete sintering of the micron-sized particles) or macropores (having diameters of several hundred microns), allowing bone growth, and introduced by techniques described in the previous section titled "Porous Ceramics of Calcium Phosphate."

The relation between compressive strength (σ_c) and the portion of the total volume occupied by pores $V_p (0 < V_p < 0.5)$ may be described with the following equation:[15]

$$\sigma_c(V_p) = 700 \exp - 5V_p \quad \text{(in MPa)}$$

A similar relation holds for tensile strength, σ_t, and microporosity V_m ($V_m < 0.05$)

$$\sigma_t(V_m) = 220 \exp - 20\ V_m \quad \text{(in MPA)}$$

It is obvious that small variations in microporosity have a much larger influence on the tensile strength than on compressive strength. Of utmost importance for (tensile) load-bearing implants is the resistance to fatigue failure. The Weibull factor, n, describes this behavior of a ceramic material in quantitative terms. Values of n = 50 to 100 are usually associated with good resistance, while values of n = 10 to 20 are clearly insufficient. Implants made of materials with such values may fail in several months of clinical use.[15] For hydroxylapatite, n = 50 in a dry environment and only 12 in a wet physiological implant bed.[16] In clinical practice, this means that calcium phosphate bioceramics can only be used (1) as small, unloaded implants, such as in the middle ear, or (2) as porous implants, in which bony ingrowth reinforces the implant, an example being a mass of ceramic particles for filling a bony defect.

BIOCOMPATIBILITY AND DEGRADATION

Since biocompatibility of calcium phosphates will be discussed elsewhere, we will limit ourselves to two aspects of a physicochemical nature, those being the importance of degradation and porosity.[10] Degradation of calcium phosphate can be explained by two processes: the first involves physicochemical dissolution and the second involves disintegration of the bulk implant into small particles.

Physiococchemical dissolution rate is governed by a number of factors:

- pH and chemical composition of incubating fluid (including composition of buffers)
- Surface per unit weight of material
- Crystallinity of the material
- Solubility product

As mentioned earlier, we have performed studies showing that for the same material (hydroxylapatite) and the same pH, dissolution rates vary considerably in different buffers. For example, Table I shows that the dissolution rate of hydroxylapatite at pH 7.2 varies from 97.4, when buffered in citrate, to 44.3 in Gomori's buffer.

Without buffers, dissolution studies yield quite different results. In addition to Klein et al.,[7] Bauer et al.[17] published data showing that, in deionized water, the pH may change from 8.6, when tricalcium phosphate is incubated, to 12.3 for tetracalcium phosphate. Since solubilities decrease rapidly with increasing pH, one expects to find a very low apparent dissolution rate for tetracalcium phosphate under such conditions. This could be the explanation for the finding by Adam et al.[5] that dissolution for tetracalcium phosphate is lower than that of hydroxylapatite.

When the same buffer is used, hydroxylapatite has a lower solubility rate than both

TABLE I
Concentration of Ca and P After 1 Week of Incubation in Various Buffers (ppm)

Material	Citrate (pH 7.2)		Gomoris (pH 7.2)		Deionized water	
	Ca	P	Ca	P	Ca	P
TCP[a]	85.0	45.9	48.9	19.6	4.6	1.7
HA[a]	97.4	43.8	44.3	17.6	5.1	2.2
TetraCP[a]	70.3	47.9	77.6	18.6	9.7	2.2
TCP[b] coating	153.0	82.5	17.1	8.0	3.3	1.5
HA[b] coating	44.0	19.8	10.8	4.25	4.4	2.3
Tetra CP[b] coating	351.0	127.5	94.4	9.0	8.8	0.20

[a] 30 mg of powder incubated in 30 ml of buffer.
[b] A coated cylinder with about 15 mg of coating incubated in 30 ml of buffer.

tricalcium phosphate and tetracalcium phosphate; however, it is not certain that this is relevant for the *in vivo* situations, where the fluids are probably saturated with respect to calcium and phosphate. There is evidence that *in vitro* dissolution studies are not representative of degradation processes *in vivo*. Animal studies by Klein[18] showed that of eight samples tested (hydroxylapatite and tricalcium phosphate, in dense, microporous, macroporous, and micromacroporous versions), only macroporous and micromacroporous tricalcium phosphate samples degraded. Of these degraded samples, particles were found in neighboring lymph nodes, thus indicating that the biological degradation process is mainly a disintegration of the implant into smaller particles, which, while being transported to neighboring tissues by phagocytes, are dissolved in part or in whole.

According to Bauer et al.,[17] there is direct contact between implant and surrounding bone for samples with a Ca/P ratio of 1:6 or higher (70 to 90% covered with bone), while tricalcium phosphate implants show hardly any direct bony contact (less than 25%). Below a ratio of 1:4, only scanty contact is found, but instead a thick soft tissue layer has been found.

Finally, we have already mentioned various types of porosities, micropores having a diameter in the order of the starting powder particles (several microns) and macropores with diameters large enough to allow bony ingrowth 100 μm or more). It has been generally recognized that long winding pores cannot be completely filled with new bone because nutrition and oxygen supply are inadequate at the far end of the pores. Therefore, a rule of thumb can be formulated, e.g., for open pores the length should not exceed ten times the width (being at least 100 μm).[19] For a particle mass, this relationship can be formulated as follows: the thickness of the layer should not exceed ten times the diameter of the particles. This explains why in larger blocks one should have large interconnecting pores and why particles of 300 μm are good for treatment of periodontal defects (maximum: several millimeters) and that larger particles (1 mm) should be used for augmenting a lower jaw up to 1 cm.

CONCLUSION

We have shown that calcium phosphate bioceramics have a rather complex chemistry although in aqueous solution only two thermodynamically stable phases exist. The phase diagrams at sintering temperatures allow the existence of many calcium phosphate compositions. Rate of cooling, exact Ca/P ratio in the starting powder, and ambient atmosphere during sintering may result in bioceramics with differing properties.

Most promising are ceramics of tricalcium phosphate (thought to be resorbable) and

hydroxylapatite and tetracalcium phosphate, of which hydroxylapatite has reached the stage of practical clinical use. Mechanically, hydroxylapatite can only withstand compressive forces. Tensile or bending forces, as are always encountered when physiologically loaded, lead to fatigue failure. Therefore, only small implants, in nonload-bearing situations such as replacements for middle ear ossicles can be used.[20] For filling defects, both (macro)porous blocks, which after several weeks are strengthened by bony ingrowth, and granular material have been successful.

Tricalcium phosphate blocks (either in the α or β form, thermodynamically both unstable under physiological conditions) resorb, probably due to disintegration into smaller particles, which are subsequently transported away to neighboring tissues. Currently, due to the fact that the resorption process is not yet quite understood, only granules to fill periodontal defects have been put on the market. Tetracalcium phosphate, calcium rich as compared with hydroxylapatite, may have good potential since the biocompatibility is about the same as for hydroxylapatite, but its enhanced calcium content may further facilitate bony ingrowth.

Of further interest are ceramics that include fluor or magnesium. Of those currently investigated, the most relevant are fluorapatite and magnesium-tricalcium phosphate.

The weak point, however, of all calcium phosphate ceramics is their susceptibility to fatigue failure. Besides reinforcement by strong filler materials, such as zirconium oxide, other techniques are currently in use, such as plasma sprayed coatings onto strong metallic surfaces and use as fillers with appropriate polymers. These topics are considered in other chapters in this volume.

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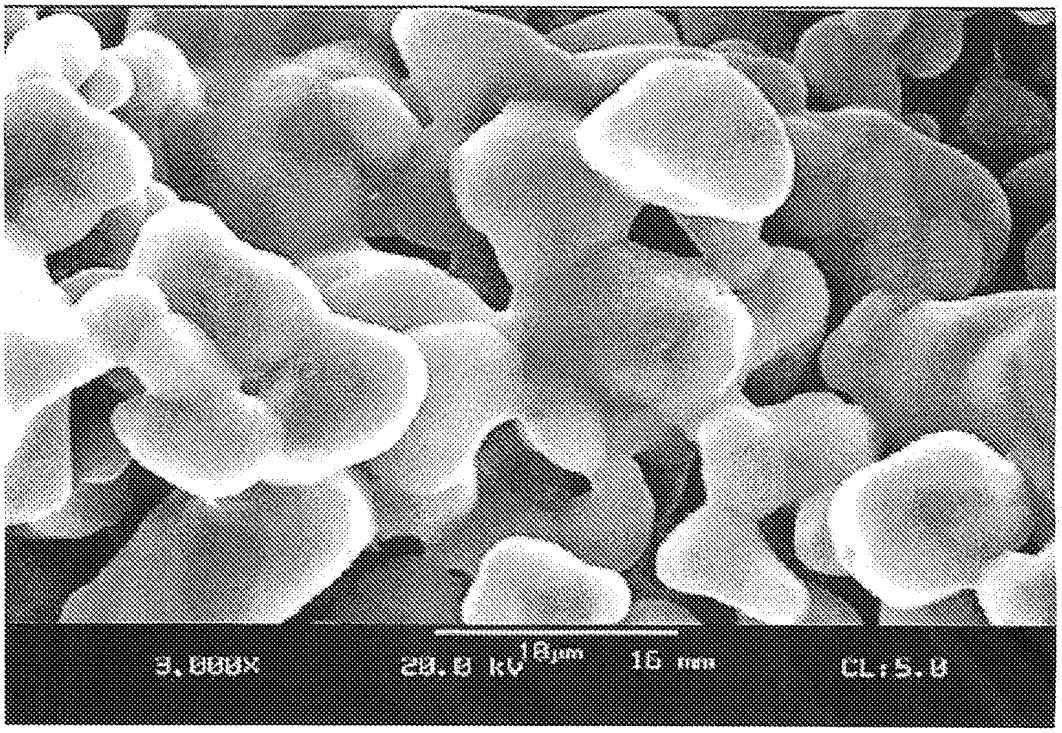
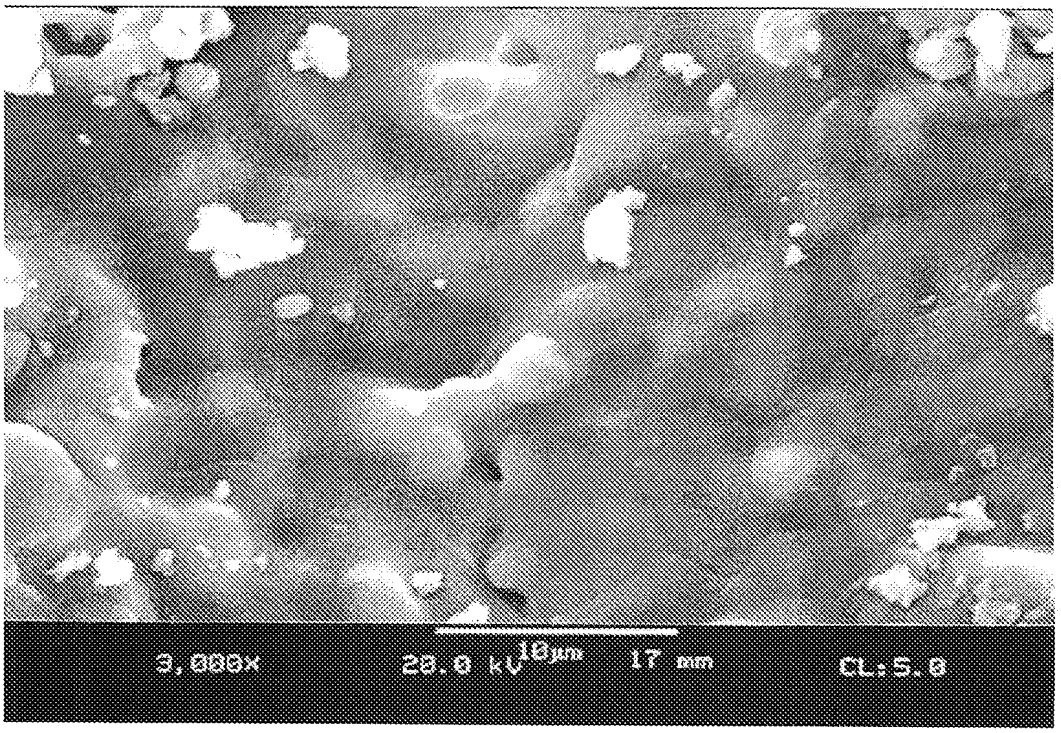
A Calcium phosphate bone formation agent according to the invention.



B Calcium phosphate after more complete sintering to obtain a more dense composition with smaller pore sizes.



ATTACHMENT II